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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,060	10/16/2003	Claudine Bruck	B45110C1	8921

7590 08/08/2006

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/687,060	BRUCK ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-53* is/are pending in the application.

4a) Of the above claim(s) *44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-43 and 45-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2005 and 16 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/16/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Office acknowledges the receipt of Applicant's election filed on 7 July 2006.

Election/Restriction

Applicant elects the species of Nef-Tat fusion orientation and TH1-inducing adjuvant with traverse. The traversal is on the grounds that doing searches on species in both genera combined would not be a significant burden on the Examiner. Applicant's traversal is partially persuasive. Each adjuvant species, however, contains a different limitation that requires a separate search. While a search of the prior art for one species may overlap with that of another species, the searches are not co-extensive and thus would be an undue burden on Office resources.

The requirement for adjuvant species election is still deemed proper and is therefore made FINAL. The requirement for fusion orientation is withdrawn.

Claims 32-53 are pending. Claim 44 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species. Claims 32-43, 45-53 are examined to the extent that they read on the elected species.

Information Disclosure Statement

An initialed and dated copy of each of Applicant's IDS form 1449, filed on 16 October 2003, is attached to the instant Office action.

Claim Rejections - 35 USC § 112, 1st ¶, new matter

Claim 41 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The limitation "wherein the protein is carboxymethylated" is nowhere recited in the original claims or specification. Since this application is filed before September 21, 2004, the preliminary amendment present on the filing date is not treated as part of the original disclosure, thus, the limitation "carboxymethylated" is treated as new matter by preliminary amendment. See MPEP §608.04(b) [R-3].

Claim Rejections - 35 USC § 112, 1st ¶, scope of enablement

Claims 32-43 and 46-53 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising Nef-wild type Tat fusion protein, does not reasonably provide enablement for a Nef-mutant Tat fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the *Wands* factors (MPEP §2164.01(a)).

Nature of the invention. The claims are drawn to an immunogenic fusion protein comprising Nef-mutant Tat.

State of the prior art. The process of site-directed mutagenesis is well known to one skilled in the art for making the claimed Tat mutant protein and Nef-mutant Tat fusion protein.

Breadth of the claims. The claims encompass any mutations in the active site and RGD motif. Therefore, the claims encompass a mutant Tat with an entirely different epitope structure around the active site and RGD motif.

Working examples. No working example of an immunogenic Nef-mutant Tat fusion protein is disclosed in the specification.

Guidance in the specification. The specification is limited to the description of only one Tat mutant (Lys41Ala, Arg78Lys, Asp80Glu) without disclosure of the immunogenic effect of this mutant Tat alone or when it is fused to the C-terminal of Nef. There is no guidance to any conserved structure or epitope conformation for maintaining the desired immunogenicity. The specification nowhere describes whether SEQ ID NO: 13, 17, or 21 comprises a wild type or mutant Tat fused to Nef.

Predictability of the art. The art lacks predictability in making mutations that will result in a desired outcome of being immunogenic and providing a protective effect (Corchero *et al.*,1996; Abaza *et al.*,1992). Cochero *et al.* (1996) discloses that the antigenic site can display different antigenicity depending on the global construction of the chimeric protein that contains VP1. Long distance influences occurring in the fusion protein can also determine the antigenic behavior of a small peptide exposed in its natural framework (Corchero *et al.* last ¶).

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, an immunogenic Nef-mutant Tat fusion protein is not considered routine in the art and, without sufficient guidance to elicit therapeutic effects, the experimentation left to those skilled in the art is to characterize every Nef-mutant Tat fusion since it is not known what immunogenic effect each mutation at the active site and RGD motif has on the fusion protein.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32-34, 37-39, and 51 are rejected under 35 U.S.C. §103(a) as being unpatentable over Schluesener (1996) in view of Hincula *et al.* (1997, see IDS filed on 16 October 2003).

The instant claims read on an immunogenic composition comprising a fusion protein of HIV Tat and Nef protein and optionally a fusion partner.

Schluesener teach linking HIV Tat to three pathogenic T-cell epitopes in admixture with a physiological saline (p.259, left column, RESULTS, 2nd ¶), which is a pharmaceutically acceptable excipient, in order to make an immunogenic composition. The reference teaches that this fusion combination improves their immunogenicity. The reference does not teach fusion of Tat with Nef.

Hinkula *et al.* teach a composition of Nef, Tat or Rev as an immunogen. The reference also teaches that due to the polymorphism found in the human population, an effective vaccine will require the combination of many proteins or glycoproteins (page 5538 last paragraph). The reference does not teach a Tat-Nef fusion protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polyvalent Tat peptide of Schluesencer by additionally fusing the Nef protein of Hincula *et al.* The skilled artisan would have been motivated to do so to increase the immunogenicity of Nef via Tat-mediated targeting of proteins, which improves cellular uptake of recombinant peptide vaccines such as Nef. There would have been a reasonable expectation of success, given that fusion with Tat peptide improves the immunogenicity of T-cell epitopes, as taught by Schluesener, and provided that Nef and Tat each can induce immune reactivity, as taught by Hinkula. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 40 is rejected under 35 U.S.C. §103(a) as being unpatentable over Schluesener (1996) in view of Hincula *et al.* (1997), and further in view of Rosin-Arbesfeld *et al.* (1994).

The instant invention is further limited to a Nef-Tat fusion protein with a Histidine (His) tail.

The relevance of Schluesener and Hincula *et al.* is set forth above. Neither reference discloses a His tail.

Rosin-Arbesfeld *et al.* suggests synthesizing a Tat protein with a His tail. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Schluesener by adding Nef protein as taught by Hincula *et al.* and a His tail as taught by Rosin-Arbesfeld *et al.* The skilled artisan would have been motivated to do so for the ease of purification of a His-tagged protein by metal affinity chromatography. There would have been a reasonable expectation of success, given the yield of protein purification and the potent activity of the purified protein, as taught by Rosin-Arbesfeld *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 42, 43, and 45-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Schluesener (1996) in view of Hincula *et al.* (1997), and further in view of Bomford *et al.* (1992).

The instant invention is further comprised of HIV gp160 or gp120 and a Th1 inducing adjuvant.

The relevance of Schluesener and Hincula *et al.* is set forth above. Neither reference discloses a HIV gp160 or gp120 fusion or an adjuvant.

Bomford *et al.* teach an immunogenic composition comprising HIV gp120 and an adjuvant, saponin, formulated with a squalene-in-water emulsion. The composition induced Th1 response in mice. See Abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Schluesener by adding Nef protein as taught by Hincula *et al.* and replacing the pathogenic peptide and formulation of Schluesener with HIV gp120 and the adjuvant formulation as taught by Bomford *et al.* The skilled artisan would have been motivated to do so to increase the immunogenicity of HIV gp120 and Nef via Tat-mediated targeting of proteins, which improves cellular uptake of recombinant peptide vaccines. There would have been a reasonable expectation of success, given the potent immune response induced in mice by the adjuvant and oil-in-water formulation of HIV gp120, as taught by Bomford *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Remarks

No claim is allowable.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP §714.02 and §2163.06.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Louise Humphrey, Ph.D.
27 July 2006

Jeffrey Parkin, Ph.D.
Primary Examiner